(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 October 2001 (25.10.2001)

PCT

(10) International Publication Number
WO 01/78729 A1

(51) International Patent Classification[7]: A61K 31/445

(21) International Application Number: PCT/US01/05826

(22) International Filing Date: 11 April 2001 (11.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/547,767 12 April 2000 (12.04.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/78729 A1

(54) **Title:** METHOD OF DOPAMINE INHIBITION USING *L-THREO*-METHYLPHENIDATE

(57) **Abstract:** This invention provides methods of effecting dopamine inhibition in a mammal by administering to the mammal *l-threo*-MPH which is substantially free from *d-threo*-MPH. Also provided by the invention are methods of inhibiting the effects of a stimulant in a mammal by administering to the mammal *l-threo*-MPH which is substantially free from *d-threo*-MPH.

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METHOD OF DOPAMINE INHIBITION USING *L-THREO*-METHYLPHENIDATE

Statement as to Federally Sponsored Research

The invention was funded, in part, by federal grants K05-MH-47370 and R-01-MH-34006. The government has certain rights in the invention.

Background of the Invention

Racemic methylphenidate (MPH) is a central nervous system stimulant that has pharmacological activity qualitatively similar to amphetamines and is widely used in the treatment of attention deficient disorder (ADD) and attention-deficient hyperactivity disorder (ADHD) (*l-threo* isomer shown in Fig. 1). Symptoms of these disorders include distractability and impulsivity; ADHD is further associated with increased activity of the body. MPH has also been used to treat cognitive defects, including dementia, that manifest in at least 70% of HIV-infected individuals who have developed Acquired Immunodeficiency Syndrome (Navia *et al.* Ann. Neurol. 1986; 19:517-524). Additionally, *d-threo*-methylphenidate is used to treat hypersomnia (Aoyama *et al.* Clin. Pharmacol. Ther., 1994; 55:270-276)

Originally MPH was sold pharmaceutically as a mixture of two racemates, 80% *dl-erthro* and 20% *dl-threo*. Subsequent studies revealed that the central stimulant activity resides in the *threo* racemate, and thus the *erythro* racemate was removed from the pharmaceutical to improve its therapeutic index.

dl-threo-MPH appears to facilitate dopaminergic and noradrenergic transmission (Maxwell *et al.* J. Pharmacol. Exp. Ther. 1970; 173:158-165; Breese *et al.*, Paychopharmacology 1975; 44:5-10; Janowsky *et al.* Eur. J. Pharmacol. 1985; 108:187-191). Patrick *et al.* found that *d-threo*-MPH produced greater induction of locomotor activity in rats and greater inhibition of tritiated dopamine and *l*-norepinephrine uptake into striatal and hypothalamic synaptosomes, respectively, than the *l*-isomer (Patrick *et al.* J. Pharmacol. Exp. Therap. 1987; 241:152-158). Additionally, Srinivas *et al.* showed that the pharmacodynamic activity of the racemic *threo*-MPH in treating ADHD resides in the *d-threo* isomer (Srinivas *et al. Clin. Pharmacol. Ther.* 1992; 52:561-568). Administration of *d-threo*-MPH instead of *dl-threo*-MPH in patients suffering from ADD, ADHD, AIDS cognitive decline, and AIDS Dementia Complex resulted in less severe side effects. These include a reduction in the euphoric effect that is produced when *dl-threo*-MPH is administered intravenously or through inhalation, to create a potential for substance abuse in patients (U.S. Patent No. 5,908,850). In rats, baboons, and humans, [^{11}C]*d-threo*-MPH demonstrated highest regional accumulation in the basal ganglia; in contrast, [^{11}C]*l-threo*-MPH displayed similar uptake in all brain regions, suggesting that its distribution in the brain is less specific. This result further supports the hypothesis that the pharmacological specificity of racemic *threo*-MPH in elevating striatal dopamine concentration resides in the *d-threo* isomer (Ding *et al. Psychopharmacology* 1997; 131:71-78; Aoyama *et al. Pharm. Res.* 1994; 11:407-411).

Summary of the Invention

The invention features a method of effecting dopamine inhibition in a mammal, such as a human, by administering an effective inhibiting amount of *l-threo*-MPH which is substantially free from *d-threo*-MPH. This method can be used for the treatment or prevention of a manic disorder, a psychotic disorder, or an anxiety disorder.

In a related aspect, the invention further includes a method of inhibiting the effect of a stimulant by administering to a mammal *l-threo*-MPH which is free from *d-threo*-MPH to a mammal. Stimulants that can be inhibited according to the invention include cocaine, amphetamines, caffeine, and *d-threo*-MPH. The methods of the invention can also be used for treating or preventing the toxic effects of an overdose of a stimulant. By "effect of a stimulant" is meant induction of dopamine or *l*-norepinephrine uptake, distractibility, impulsivity, or hyperactivity.

l-threo-MPH is administered orally, intramuscularly, intravenously, or subcutaneously to the mammal. *l-threo*-MPH generally is administered together with a pharmaceutically acceptable carrier. Generally, dosage is in the same range as the dosage currently used for *d-threo*-MPH.

Brief Description of the Drawings

Fig. 1 is the structure of *l-threo*-MPH [(S,S(-)-*threo*-methylphenidate].

Fig. 2 is a graph that shows the inhibition by *l-threo*-MPH of locomotor behavioral arousal in rats (N=6/dose of *l-threo*-MPH) treated with a fixed dose of *d-threo*-MPH [3 mg/kg, intraperitoneally (i.p.)]. The ID_{50} of *l-threo*-MPH is approximately 2.5 mg/kg, i.p..

Fig. 3 is a graph that shows the inhibition by *l-threo*-MPH of locomotor behavioral arousal in rats (N=6/dose) treated with a fixed dose of the stimulant cocaine-HCl (3 mg/kg, i.p.). The ID_{50} of by *l-threo*-MPH is approximately 2.0 mg/kg, i.p..

Fig. 4 is a graph that shows the inhibition by *l-threo*-MPH of locomotor behavior arousal in rats (N=6/dose) compared to a fixed dose of the direct dopamine agonist R(-)-apomorphine-HCl (1 mg/kg, i.p.). The ID_{50} of *l-threo*-MPH is approximately 2.5 mg/kg, i.p..

Detailed Description

We have found that the *d-threo*-isomer of MPH is more than twice as potent as the clinically used *dl*-racemic mixture. We believe that the *l*-isomer interacts antagonistically with the pharmacologically active *d*-isomer.. This novel finding was supported by the reduction in spontaneous locomotion in rats treated with *d-threo*-MPH after administration of *l-threo*-MPH (Fig. 2).

l-threo-MPH was also shown to inhibit the stimulant effects of other indirect or direct dopamine agonists. Specifically, *l-threo*-MPH displayed potent, dose-dependent inhibition of locomotion in rats induced by a fixed dose of the stimulant, indirect dopamine agonist cocaine (Fig. 3) or the classic direct dopamine agonist R(-)-apomorphine (Fig. 4). The aforementioned findings indicate that *l-threo*-MPH acts as an antagonist of central nervous system dopaminergic activity. Accordingly, the invention features a method for the treatment or prevention of a manic disorder, a psychotic disorder, or an anxiety disorder in a mammal such as a human patient, by administering to the mammal a pharmaceutically effective amount of *l-threo*-MPH substantially free of the *d-threo* isomer. Additionally, the invention includes a method for inhibiting the effect of a stimulant by administering the substantially pure *l-threo*-MPH

isomer to a mammal.

The following example is to illustrate the invention; it is not meant to limit the invention in any way.

Inhibition of Locomotor Activity by *l-threo*-MPH

Young adult albino rats (Charles River CD-VAF, 200-300 g body weight) were injected with test drug or vehicle, and tested singly in their home cages between 10:00 and 16:00 hours to minimize the effects of circadian variations in behavioral responses. Six rats were tested per condition and compared to 18 pooled controls. *l-threo*-MPH was tested at doses of 0, 0.3, 1.0, 3.0, and 10.00 mg/kg [0.429, 1.29, 4.29, 12.9, and 42.9 μmole/kg intraperitoneally (i.p.)] at a volume of 1.0 mg/kg, in physiological saline (150 mM NaCl in purified water) as the vehicle, in rats given fixed doses of the stimulant *d-threo*-MPH (3 mg/kg, i.p.), the stimulant cocaine-HCl (3 mg/kg, i.p.), or the direct dopamine agonist R(-)-apomorphine-HCl (1 mg/kg, i.p.). Locomotion, as an index of behavioral arousal, was recorded in a Stoelting 12-channel electronic activity monitor (Wood Dale, IL) controlled by an Apple Macintosh microcomputer. Sensors were placed in an electrically-shielded and grounded, sound-attenuated enclosure to minimize environmental artifacts, spaced at least 50 cm apart to prevent radiofrequency coupling, and adjusted to respond to locomotion selectively and exclude small movements such as grooming and chewing. Sensor responses were frequently recalibrated and standardized using a pendulum. Locomotor activity data were accumulated and analyzed every 5 minutes over a 60 minute testing session, using the MacLab computer software system (ADInstruments, Castle Hill, NSW, Australia) for the Macintosh microcomputer. The raw data were entered into a Microsoft Excel spread sheet, transferred to a StatView spreadsheet, analyzed

by 2-way ANOVA with post-hoc Scheffé tests with SAS StatView-V programs, and displayed as dose-effect plots with Cricket Graph software. All of the doses of *d-threo*-MPH, cocaine, and apomorphine tested increased locomotion markedly, from a saline basal level of 0.122 ± 0.007 activity units/hour to 0.692 ± 0.077 (5.68-fold increase), 1.25 ± 0.07 (10.3 fold increase), and 1.18 ± 0.08 (9.78-fold increase) units/hour, respectively. *l-threo*-MPH inhibited all three of these stimulants. The dose response curves of *l-threo*-MPH inhibition of locomotion in rats stimulated by *d-threo*-MPH, cocaine, or apomorphine are shown in Fig 2, 3, and 4, respectively. The potency of *l-threo*-MPH (ID_{50}) calculated from these graphs is approximately 2.5, 2.0, or 2.5 mg/kg, respectively.

What is claimed is:

1. A method of effecting dopamine inhibition in a mammal, said method comprising administering to said mammal *l-threo*-MPH which is substantially free from *d-threo*-MPH.

2. The method of claim 1, wherein said method is used for the treatment or prevention of a manic disorder.

3. The method of claim 1, wherein said method is used for the treatment or prevention of a psychotic disorder.

4. The method of claim 1, wherein said method is used for the treatment or prevention of an anxiety disorder.

5. A method of inhibiting the effects of a stimulant in a mammal, said method comprising administering to said mammal *l-threo*-MPH which is substantially free from *d-threo*-MPH.

6. The method of claim 5, wherein said stimulant is cocaine.

7. The method of claim 5, wherein said stimulant is an amphetamine.

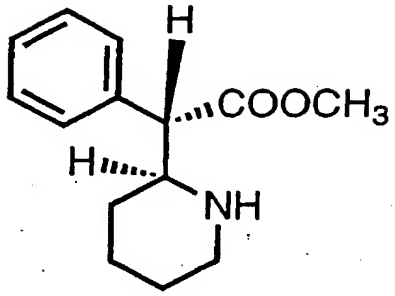
8. The method of claim 5, wherein said stimulant is methcathinone.

9. The method of claim 5, wherein said stimulant is caffeine.

10. The method of claim 5, said method comprising treating or preventing the toxic effects of an overdose of said stimulant.

11. The method of claim 1, wherein *l-threo*-MPH is administered orally, intramuscularly, intravenously, or subcutaneously to said mammal.

12. The method of claim 11, wherein *l-threo*-MPH is administered together with a pharmaceutically acceptable carrier.



S,S-(–)-*threo*-Methylphenidate
(MW = 233.31)

Fig. 1

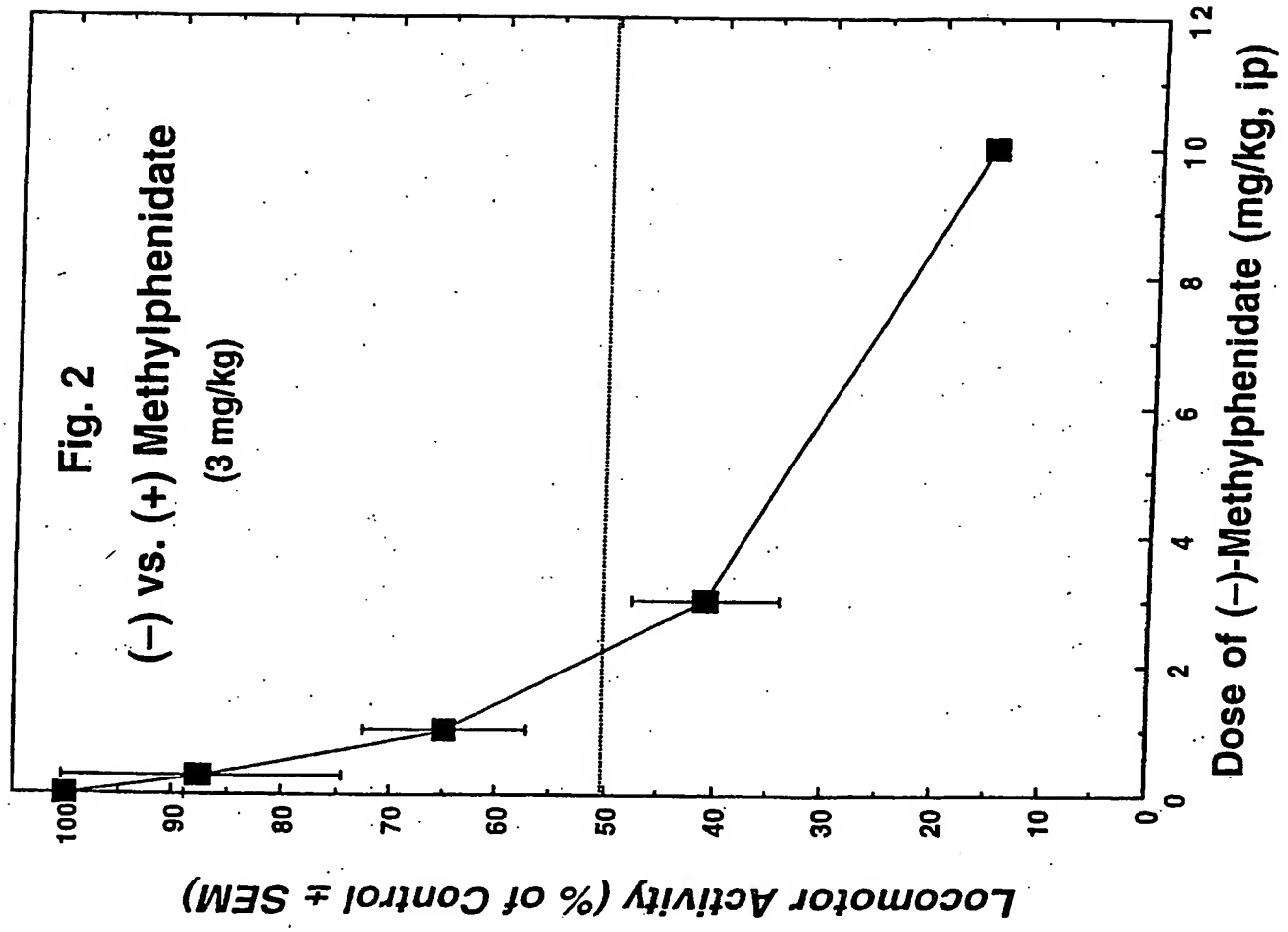


Fig. 2
(–) vs. (+) Methylphenidate
(3 mg/kg)
Locomotor Activity (% of Control ± SEM)
Dose of (–)-Methylphenidate (mg/kg, ip)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12

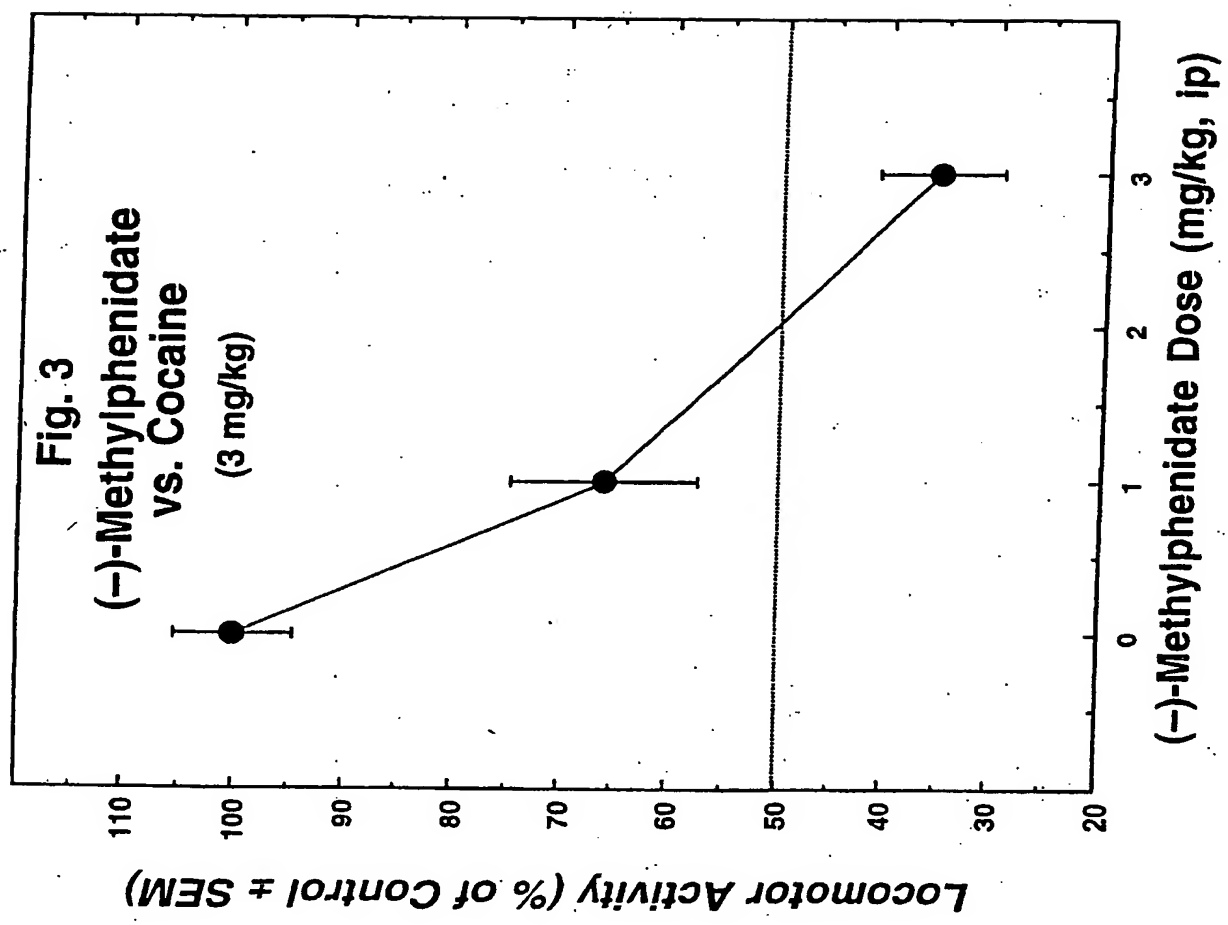


Fig. 3
(-)-Methylphenidate
vs. Cocaine
(3 mg/kg)
Locomotor Activity (% of Control ± SEM)
110
100
90
80
70
60
50
40
30
20
0
1
2
3
(-)-Methylphenidate Dose (mg/kg, ip)

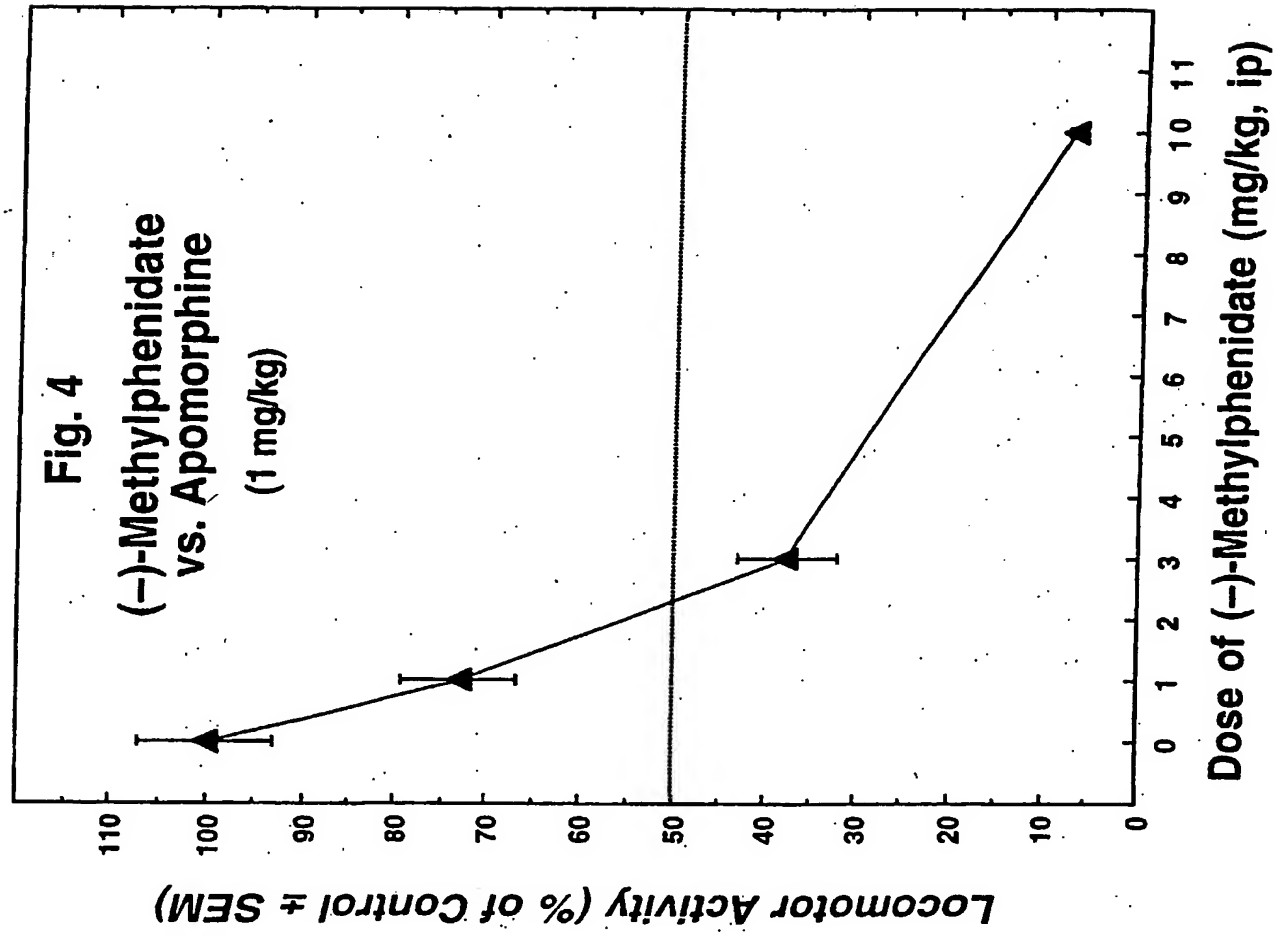


Fig. 4
(–)-Methylphenidate
vs. Apomorphine
(1 mg/kg)
Locomotor Activity (% of Control ± SEM)
Dose of (–)-Methylphenidate (mg/kg, ip)
0
10
20
30
40
50
60
70
80
90
100
110
0 1 2 3 4 5 6 7 8 9 10 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/05826

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/445
US CL :514/317
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/317

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,874,090 A (BAKER et al) 23 February 1999, see entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
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Date of the actual completion of the international search	Date of mailing of the international search report
15 JUNE 2001	31 JUL 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer WILLIAM JARVIS
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Form PCT/ISA/210 (second sheet) (July 1998) *

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/05826

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

BRS:WEST (USPAT, EPAB, JPAB, DWPI); STN (REG, CA, BIOSIS, MEDLINE, DRUGU, EMBASE)
search terms: l-threo-methylphenidate, manic, mania, psychosis, psychotic, antipsychotic, anxiety, schizophrenia, stimulant, cocaine, amphetamine, methcathinone, caffeine, addiction, dependence, abuse